

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 250 852 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
23.10.2002 Bulletin 2002/43

(51) Int Cl.⁷: **A23L 1/03, A23D 9/007**

(21) Application number: **02075966.8**

(22) Date of filing: **13.03.2002**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **09.04.2001 EP 01201296**

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BE CH DE DK ES FI FR GR IT LI NL PT SE AT
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Designated Contracting States:
GB IE

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(54) **Concentrate of triterpenes**

(57) The invention concerns concentrates of ursolic acid or its salts and oleanoic acid, wherein

- (i) ursolic acid and oleanoic acid or its salts are present in an total amount for the two of more than 22 wt %, preferably 30 to 65 wt %
- (ii) sugar residues are present in an amount of less than 40 wt %, preferably less than 25 wt %, in particular in an amount of 1 to 10 wt %
- (iii) while ursolic acid and oleanoic acid or its salts are present in a weight ratio of more than 3.6, pref-

erably 4.0 to 6.0

(iv) the balance being other materials, including glycerides and / or triterpenes other than ursolic acid and oleanoic acid and a method to make these concentrates.

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Description

[0001] Ursolic acid and oleanolic acid are well known compounds that can be isolated from a number of fruit skins. A typical example of fruit skins that can be applied are apple skins, but more sources are disclosed in e.g. col.2, 1.16-20 of US 5 948 460. In literature (cf e.g. JP 09/020674 or SU 827066 or de Sousa Menezes in Anais da Bras de Cincias, Acad Brasileira de Cincias, Rio de Jan vol 70, 1998, p.761 or Bock c.s in Die Nahrung vol 10, 1966, p.409 or Croteau in Phytochem vol 8, 1969, p.219) a standard procedure for isolating ursolic acid and / or oleanolic acid from fruit skins is to perform an extraction of the skins with an organic solvent such as acetone or ethanol. However the results of the prior art techniques were found to be unsatisfactory for a number of reasons. It was found that the products obtained had a severe off taste which prevented their use in food products. Further the compounds could only be obtained in low yields, which was probably due to the presence of high amounts of unidentified organic compounds in the fruit skins, possibly being monomolecular and higher molecular sugar residues, which makes the working-up of the extraction product very difficult. Further it was found that the purity of the products obtained was far below what is considered as acceptable for use in foods while the products also had an undesired greenish colour which made them less acceptable for use in food products that should have a light or bland colour.

We therefore studied whether we could find ways to overcome above disadvantages and to come to concentrates of ursolic acid and oleanolic acid that do not display these disadvantages.

[0002] This study resulted in the finding of novel concentrates that comprise relatively large amounts of ursolic acid and oleanolic acid or their food acceptable salts such as their alkali or alkali earth metal salts and that could be used in foods directly without the disadvantages of the known concentrates. Therefore our invention concerns in the first instance a concentrate comprising ursolic acid and oleanolic acid or their food acceptable salts in substantial amounts, wherein the concentrate comprises:

- (i) ursolic acid and oleanolic acid or their food acceptable salts in an total amount for the two of more than 22 wt %, preferably 30 to 65 wt %
- (ii) sugar residues in an amount of less than 40 wt %, preferably less than 25 wt %, in particular in an amount of 1 to 10 wt %
- (iii) while ursolic acid and oleanolic acid or their salts are present in a weight ratio of more than 3.6, preferably 4.0 to 6.0
- (iv) the balance being other materials, including glycerides and / or triterpenes other than ursolic acid and oleanolic acid.

The sugar residues can comprise mono-molecular sugars such as glucose and fructose but also di-molecular carbohydrates such as sucrose and even oligomers of carbohydrates. Preferred products are those products wherein the other materials (iv) are present in amounts of 15 to 65 wt %, more preferably 25 to 50 wt %. These other materials comprise glycerides and other triterpenes, in particular the other materials comprise 1 to 40 % glycerides and for the rest other triterpenes which other terpenes comprise maslinic acid and / or pomolic acid and / or pirolonic acid

[0003] Food products containing the novel concentrates are also part of the invention and thus the invention also covers food products comprising an effective amount of the concentrate according to claims 1 to 3 so that the food product can deliver by a normal daily consumption of the food product 10 to 100 % of the recommended daily amount of ursolic acid and oleanolic acid. Recommended daily amounts can range from 10 mg to 4 gram per kilogram human body weight depending on the type of deficiency that is intended to be treated with the use of the food product as health component. The effective amount being that amount that displays a noticeable effect of the consumption of the health component.

The novel concentrates can also be used in the form of food supplements and therefore our invention also concerns food supplements comprising the concentrate according to the invention in encapsulated form. The concentrates can be encapsulated in food grade or food acceptable materials, in particular the encapsulating material used hereof is selected from the group consisting of sugars, starches, modified starches, hydrocolloids, gums and gelatin

[0004] In order to enable an economic and feasible route to isolate a useful concentrate of ursolic acid and oleanolic acid from natural waste materials we developed a new process. This process led to higher yields of the desired active components (ursolic acid and oleanolic acid present in this waste material) while simultaneously these active components were obtained in purer form than achievable so far. Thus according to another embodiment of our invention our invention also concerns a method for producing a concentrate with the composition according to the invention by:

- (i) selecting a natural material comprising ursolic acid and oleanolic acid in sufficient amounts
- (ii) drying to a water level of less than 10 wt % of either

- a) the natural material of step (i) or
- b) milled or ground wet material of step (iii a)

(iii) milling or grinding of either

- a) the wet natural material of step (i) or
- b) the dried natural material of step (ii a),

(iv) extracting of either

- a) the milled or ground material resulting from step (iii b) or
- b) the milled or ground material from step (ii a)

with an organic solvent, preferably being acetone, ethyl acetate or ethanol and collecting an extract of the final concentrate in the solvent

(v) removing the solvent from the extract obtained after step (iv a) or step (iv b).

[0005] In those instances wherein the food acceptable salts are desired the above extract can be treated with a base and the salts can be isolated.

[0006] Although above process already resulted in better products and higher yields we found that these products and yields could be further improved if step (ii) or step (iii) is either preceded or followed by a wash with an aqueous solution, followed in case a wet product is obtained by a drying, which aqueous solution preferably is applied in a weight ratio between aqueous solution and natural material of more than 2 to 1, preferably 5 : 1 to 30 : 1

[0007] Further improvements were obtained if the aqueous solution is a solution of a base and preferably has a pH of 8 to 12 or if the aqueous solution is an acidic solution, preferably with a pH = 0 to 2. The best results were obtained by performing a process wherein the milling is preceded or followed by a treatment with acid and with base (or the other way round) using an intermediate wash until about neutral. So a combined base / acid treatment is used, however the order of these treatments was found to be irrelevant.

[0008] Although many different sources of starting materials can be used in our process we found that the best results were obtained when using a cheap and easily available starting material in the form of apple skins.

[0009] We further noticed that the particle size of the products obtained after our milling or grinding step(s) also had an impact on the efficiency of our process. It was found that the best results were obtained if the milling or grinding is performed until particles are obtained with a particle size of less than 20 mm, preferably 2 to 20 mm.

[0010] Another important product parameter is the temperature during the aqueous wash. It was found that the best results were obtained when using a temperature of at least 35 °C, in particular at least 70 °C.

[0011] The concentrates that we obtained can be used in food products for many different purposes. They e.g. can be applied in order to provide the food product with the health function known for ursolic acid resp. oleanolic acid. However we also found that these components had an impact on the crystallisation behaviour of the fat present in a food product. Therefore our invention also concerns according to a last embodiment the use of a concentrate of ursolic acid and oleanolic acid or its salts with the composition according to the invention wherein the concentrate is used to modify the crystallisation behaviour of a fat or a fat blend in a final food product to:

- (i) increase the hardness of a fat blend or the final product and / or
- (ii) to improve the plasticity of the fat blend or final product and / or
- (iii) to improve the oral mouthfeel of the fat blend or the final product and / or
- (iv) to improve the heat resistance of the fat blend or the final product and / or
- (v) to improve the speed of crystallisation of the fat blend or the final product and / or
- (vi) to increase the aeration properties of the fat blend or the final product and / or
- (vii) to decrease drying times of ice cream coatings

EXAMPLES

Example 1

[0012] This example shows the benefit of a single/combined pretreatment of apple skins on the amount and purity of ursolic acid concentrate.

[0013] Skins from apples were dried in a drying cabinet at 70°C until the residual moisture amounted <3%. From

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3000 gram wet skins 900 gram dried material was collected. This material was milled in a Retch mill provided with a sieve of 1.5 mm. All material passed this sieve prior to the pretreatment. The milled skins were pretreated in various ways. The single pretreatments were:

Water,
0.05 M Na₂CO₃,
0.1N HCL,
0.2M H₃PO₄

[0014] The combined pretreatment was:

0.2M H₃PO₄ followed by 0.05M Na₂CO₃

Single pretreatment

[0015] 90 gram dried and milled apple skins were suspended in 1800 g demineralized water. The mixture was poured in a double walled vessel of 2 l provided with stirrer and thermometer. The stirrer was set at 500 rpm, the temperature within the vessel was held at 98°C. After 8 h at 98°C the suspension was cooled to 30°C and collected in two centrifugal flasks. The suspension was centrifuged at 3000 rpm for 15 minutes. The clear upper layer was decanted and discarded, the sediment was spreaded on dishes and dried in a drying cabinet at 70°C until the residual moisture amounted <3%. The dried pretreated skins were milled in a Retch mill provided with a sieve of 1.5 mm.

[0016] Instead of demineralized water also pretreatments were carried out with acidic or alkaline solutions. The conditions were:

1710 ml 0.1M HCL 6h at 98°C
1710 ml 0.05M Na₂CO₃ 4h at 98°C
1710 ml 0.2M H₃PO₄ 6h at 98°C.

Combined pretreatment

[0017] Additionally to the single pretreatment with 0.2M H₃PO₄, a second pretreatment was carried out with 0.05M Na₂CO₃. For that purpose 90 gram dried and milled apple skins was suspended in 1686 ml demineralized water and 24 ml H₃PO₄ (85%). The mixture was poured in a double walled vessel of 2 l provided with stirrer and thermometer. The stirrer was set at 500 rpm, the temperature within the vessel was held at 98°C. After 6 h at 98°C the suspension was cooled to 30°C and collected in two centrifugal flasks. The suspension was centrifuged at 3000 rpm for 15 minutes. The clear upper layer was decanted and discarded, the sediment was spreaded on dishes and dried in a drying cabinet at 70°C until the residual moisture amounted <3%. The dried pretreated skins were milled in a Retch mill provided with a sieve of 1.5 mm.

[0018] Phosphoric acid treated skins were subjected to an additional treatment with 0.05M Na₂CO₃. 40 g of this material was suspended in 760 g demineralized water and the pH was adjusted to 7.0 with concentrated sodium hydroxide. 4 g Na₂CO₃ was added and dissolved. The suspension was stirred at 500 rpm at 98°C for 4 h. The suspension was centrifuged at 3000 rpm for 15 minutes. The clear upper layer was decanted and discarded, the sediment was spreaded on dishes and dried in a drying cabinet at 70°C until the residual moisture amounted <3%. The dried pretreated skins were milled in a Retch mill provided with a sieve of 1.5 mm.

Extraction

[0019] Approximately 18 grams of dried and milled skins (water<3%) were put in a Soxhlet extraction equipment and extracted with acetone. The extraction lasted 3 hours. During that time 18 repetitions per extraction took place. Acetone was almost completely removed by means of a vacuum rotation evaporator. The last traces of acetone were removed by putting the roundbottomflask in a water bath at 80°C and maintaining this to a vacuum pump at 2 mbar for 1 h. The crude acetone extract was weighed and analysed by gas-chromatography.

Analyses

[0020] Crude acetone samples (powder) are first silylated with BSTFA at 70°C for 4h, thereafter dissolved in hexane and then injected in the GC. The conditions of the GC were:

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Column:	CP-Sil 5 CB 10m *0.32 mm Df=0.12 carriergas He
Inj. amount:	1 ul
inj. type:	cool on column sec cooling time 10 s
Pressure:	30 kPa
Temp inj.	80°C temp interface 250°C
ovenprog	80°C (2 min)-10°C/min - 360°C (15 min)

Results of example 1

sample	amount (g) of extract from 100 g skins	amount triter-pene acids/ 100 g skins	Composition of acetone extract (%)					
			triterpene acids		High Mol. Weight triterp. acids	TAGs	sugars	others
			Ursolic	Oleanoic				
no pretreatment	21.2	5.5	21.1	4.7	14.8	8.6	27.8	23.1
water 98C	20.2	7.9	32.1	7.2	22.2	10.0	7.5	21.0
0.05 M Na ₂ CO ₃	19.4	8.6	36.6	7.8	19.1	10.9	2.4	23.2
0.1 M HCL	28.0	10.9	31.6	7.4	16.1	12	6.6	26.3
0.2 M H ₃ PO ₄	29.8	7.8	21.8	4.3	11.8	8.8	4.5	48.8
combined: 0.2M H ₃ PO ₄ +0.05M Na ₂ CO ₃	22.4	10.0	37.1	7.5	17.6	12.2	3.0	22.6

Example 2

[0021] This example shows the benefit of milling apple skins on the extractable amount of ursolic acid.

[0022] Skins from apples were dried in a drying cabinet at 70°C until the residual moisture amounted <3%. From 898 gram wet skins 274 gram dried material was collected. The water content amounted 2.8%. The batch dried skins was divided into four parts of each 68.5 g. A Retsch mill was applied to mill the skins. The mill has a rotor of 24 teeth and can used with or without a sieve. Each portion was milled differently using different sieves. The first sample (un-milled) was extracted as such. The second sample (crushed) was milled without a sieve. These particles have a diameter of 3-5 mm. The third sample (1.5 mm) was obtained by applying a sieve of 1.5 mm. All skins passed this sieve. The fourth sample (0.2 mm) was obtained by applying a sieve of 0.2 mm.

Extraction

[0023] Acetone extraction was carried out according to the method mentioned in example 1

Analyses

[0024] GC-FID analyses was carried out according to the method mentioned in example 1

Results of example 2								
sample	amount (g) of extract from 100 g skins	amount triterpene acids/ 100 g skins	Composition of acetone extract (%)					
			triterpene acids		High Mol. Weight triterp. acids	TAGs	sugars	others
			Ursolic	Oleanoic				
no milling	15.0	3.0	15.4	4.4	16.0	0.6	44.2	19.4
crushed	19.1	3.2	13.0	3.9	13.1	3.5	47.4	19.1
1.5 mm	22.6	3.6	12.4	3.4	12.5	6.9	46.9	18.1
0.2 mm	27.9	4.9	13.8	3.8	14.2	9.7	41.4	17.1

Example 3

[0025] This example shows the results of a combined pretreatment carried out on natural apple skins with minimal processing. The benefit is shown on the amount and purity of the crude acetone extract. There are two process variants.

- a: milling with water, acid and alkaline pretreatment followed by drying
- b: acid and alkaline pretreatment, followed by drying and milling

[0026] Both process variants will be outlined.

Variant a:

[0027] 300 g natural apple skins were mixed with 1676 ml demineralized water and 24 ml H₃PO₄ (85%). The pH was 1.5. The mixture was poured in a double walled vessel of 2 l provided with stirrer and thermometer. The stirrer was set at 500 rpm, the temperature within the vessel was held at 98°C. After 6 h at 98 °C the suspension was cooled to 30°C, neutralised with concentrated NaOH to pH 7 and collected in two centrifugal flasks. The suspension was centrifuged at 3000 rpm for 15 minutes. The clear upper layer was decanted and discarded, the sediment was returned in the vessel. 1700 g water and 9.0 g Na₂CO₃ was added to the vessel and the mixture was stirred for 4 h at 98°C. The skins were cooled to 30°C, and collected in two centrifugal flasks and centrifuged at 3000 rpm for 15 minutes. The clear layer was discarded the sediment was spreaded on dishes and dried in a drying cabinet at 70°C until the residual moisture amounted <3%. The dried pretreated skins were milled in a Retch mill provided with a sieve of 1.5 mm.

Variant b:

[0028] 300 g natural apple skins were mixed with 1676 ml demineralized water and the mixture of skins and water was milled through a colloid mill (Prestomill PM30). The mixture was poured in a double walled vessel of 2 l provided with stirrer and thermometer. 24 ml of concentrated H₃PO₄ (85%) was added. The stirrer was set at 500 rpm, the temperature within the vessel was held at 98°C. After 6 h at 98 °C the suspension was cooled to 30°C, neutralised with concentrated NaOH to pH 7 and collected in two centrifugal flasks. The suspension was centrifuged at 3000 rpm for 15 minutes. The clear upper layer was decanted and discarded, the sediment was returned in the vessel. 1700 g water and 9.0 g Na₂CO₃ was added to the vessel and the mixture was stirred for 4 h at 98°C. The skins were cooled to 30°C, and collected in two centrifugal flasks and centrifuged at 3000 rpm for 15 minutes. The clear upper layer was discarded, the sediment was spreaded on dishes and dried in a drying cabinet at 70°C until the residual moisture amounted <3%.

Extraction

[0029] Acetone extraction was carried out according to the method mentioned in example 1

Analyses

[0030] GC-FID analyses was carried out according to the method mentioned in example 1

Results of example 3								
sample	amount (g) of dried skins from 300 g wet skins	yield of acetone extract from treated skins (%)	Composition of acetone extract (%)					
			triterpene acids		High Mol. Weight triterp. acids	TAGs	sugars	others
			Ursolic	Oleanolic				
variant a	35.9	21.0	38.9	8.0	16.3	10.0	0.3	26.5
variant b	36.4	17.6	38.7	8.1	17.0	7.2	0.6	28.4

[0031] Another effect of the alkaline pretreatment was observed with respect to the improved organoleptical properties. The alkaline treated material showed a significant lighter colour and less off-flavour.

Claims

1. Concentrate comprising ursolic acid and oleanolic acid derivatives in substantial amounts, wherein the concentrate comprises:

(i) ursolic acid and oleanolic acid or food acceptable salts thereof in an total amount for the two of more than 22 wt %, preferably 30 to 65 wt %

(ii) sugar residues in an amount of less than 40 wt %, preferably less than 25 wt %, in particular in an amount of 1 to 10 wt %

(iii) while ursolic acid and oleanolic acid or their salts are present in a weight ratio of more than 3.6, preferably 4.0 to 6.0

(iv) the balance being other materials, including glycerides and / or triterpenes other than ursolic acid and oleanolic acid.

2. Concentrate according to claim 1 wherein the other materials (iv) are present in amounts of 15 to 65 wt %, more preferably 25 to 50 wt %

3. Concentrate according to claims 1 and 2 wherein the other materials comprise 1 to 40 % glycerides and for the rest other triterpenes which other terpenes comprise maslinic acid and / or pomolic acid and / or pirolonic acid

4. Food products comprising an effective amount of the concentrate according to claims 1 to 3 so that the food product can deliver by a normal daily consumption of the food product 10 to 100 % of the recommended daily amount of ursolic acid and oleanolic acid

5. Food supplements comprising the concentrate according to claims 1 to 3 in encapsulated form

6. Food supplements according to claim 5 wherein the encapsulating material is selected from the group consisting of sugars, starches, modified starches, hydrocolloids, gums and gelatin

7. Method for producing a concentrate with the composition according to claims 1 to 3 by:

(i) selecting a natural material comprising ursolic acid and oleanolic acid in sufficient amounts

(ii) drying to a water level of less than 10 wt % of either

- a) the natural material of step (i) or
- b) milled or ground wet material of step (iii a)

(iii) milling or grinding of either

- a) the wet natural material of step (i) or
- b) the dried natural material of step (ii a),

(iv) extracting of either

- a) the milled or ground material resulting from step (iii b) or
- b) the milled or ground material from step (ii a)

with an organic solvent, preferably being acetone , ethyl acetate or ethanol and collecting an extract of the final concentrate in the solvent

(v) removing the solvent from the extract obtained after step (iv a) or step (iv b).

8. Method according to claim 7 wherein step (ii) or step (iii) is either preceded or followed by a wash with an aqueous solution, followed in case a wet product is obtained by a drying, which aqueous solution preferably is applied in a weight ratio between aqueous solution and natural material of more than 2 to 1, preferably 5 : 1 to 30 : 1

9. Method according to claim 8 wherein the aqueous solution is a solution of a base and preferably has a pH of 8 to 12

10. Method according to claim 8 wherein the aqueous solution is an acidic solution, preferably with a pH = 0 to 2

11. Method according to claim 7 wherein the milling or grinding is preceded or followed by a treatment with acid and with base (or the other way round) using an intermediate wash until about neutral.

12. Method according to claims 7 to 11 wherein the natural material is washed with an organic solvent, preferably acetone , ethyl acetate or ethanol, prior to subjecting it to any of steps (ii) or (iii) of the process according to claim 7

13. Method according to claims 7 to 12 wherein the natural material is formed by the skins of apples

14. Method according to claims 7 to 13 wherein the milling or grinding is performed until particles with a particle size of less than 20 mm, preferably 2 to 20 mm are obtained.

15. Method according to claims 7 to 13 wherein the wash with the aqueous solution is performed at a temperature of at least 35 °C., preferably at least 70 °C.

16. Use of a concentrate of ursolic acid and oleanolic acid or its salts with the composition according claims 1 to 3 wherein the concentrate is used to modify the crystallisation behaviour of a fat or a fat blend in a final food product to:

- (i) increase the hardness of a fat blend or the final product and / or
- (ii) to improve the plasticity of the fat blend or final product and / or
- (iii) to improve the oral mouthfeel of the fat blend or the final product and / or
- (iv) to improve the heat resistance of the fat blend or the final product and / or
- (v) to improve the speed of crystallisation of the fat blend or the final product and / or
- (vi) to increase the aeration properties of the fat blend or the final product and / or
- (vii) to decrease drying times of ice cream coatings.



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EUROPEAN SEARCH REPORT

Application Number
EP 02 07 5966

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : prior art document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03/02 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
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